U.S.S.N.: 09/699,003
Filed: October 26, 2000
AMENDMENT

## Remarks

**Rejections under 35 U.S.C. 112, indefiniteness**

Claims 1-6, 8-10, and 20 23 were rejected under 35 U.S.C. 112, as indefinite. These rejections are respectfully traversed if applied to the amended claims.

Claim 1 has been amended to state that the amount is reduced relative to the value prior to treatment. Claims 12 and 20 have been amended to reference "blood or blood component" to provide clear antecedent basis for plasma.

**Double Patenting Rejections**

Claims 1-4, 8-10, 12, and 16-20 were rejected under the doctrine of obviousness type double patenting over claims 1-4, 6-8, 10, 14 and 16-18 of U.S. patent No. 6,231,536, U.S. Patent No. 6,620,382, and U.S.S.N. 09/709,045. Although the undersigned strongly disagrees with this rejection, Terminal Disclaimers with Forms under 37 C.F.R. 3.73(b) and the fees for a small entity are enclosed solely to facilitate prosecution and Declaration of an Interference.

**Rejections under 35 U.S.C. 103**

Claims 1-4, 8, 12, and 20 were rejected under 35 U.S.C. 103(a) as obvious over U.S. Patent No. 4,708,713 to Lentz in view of Selinsky, et al., Immunology 94:88-93 (1998). Claims 9, 10 and 16-19 were rejected over Lentz and Selinsky and further in view of U.S. Patent No. 5,523,096 to Okarma, et al. **Claims 5 and 6 were rejected as obvious over Lentz and Selinksky in view of Feinman, et al. Claims 1-4, 5, 6, 9-10, 12 and 16-20 were rejected as obvious over Selinksky and Van Zee, et al. in combination with Lentz and U.S. Patent No. 6,017,527 to Maraskovsky. THESE REJECTIONS CAN NOT BE RESPONDED TO SINCE NO CITATION NOR COPY OF THE REFERENCES WERE PROVIDED.** These rejections are respectfully traversed.

*The Claimed Invention*

Applicant has discovered that it is possible to treat a disease such as cancer by selectively removing small molecular weight inhibitors that are produced by the cancerous cells to block the patient's immune system from killing the tumor.

The treatment is now in clinical trials in Europe, with extremely promising results, having produced remissions in a number of patients who had failed traditional chemotherapy and radiation treatments. Promising results have also been obtained in the treatment of patients with autoimmune disease such as multiple sclerosis.

It has long been believed that tumors must produce some type of blocking agent, that allowed the tumor(s) to grow, ultimately killing the patient. Traditional chemotherapy is based on the premise that one administers a cytotoxic agent that kills the more rapidly proliferating tumor cells at a higher rate than the normal cells. The disadvantages of this are immediately apparent – if the tumor cells are slow growing, chemotherapy is ineffective. If the cells become resistant, the chemotherapy is ineffective. In all cases, there is serious toxicity and other side effects.

Targeted chemotherapy was developed as an obvious corollary, targeting the toxic agent to a marker on the tumor cells but not on the normal cells. While this produced better results, it has been difficult to find a marker that could be targeted in all cases.

Many tumor markers are known. Two that are used as diagnostics, to indicate how much cancer is present, include prostate specific antigen ("PSA") and carcinoembryonic antigen ("CEA"). Studies to determine if one could target these antigens, or induce remission by removing them, failed.



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Applicant arrived at his claimed method after many years. When he first started treating patients, he believe that the agent produced by the tumors was a large immunoglobulin complex, so he treated plasma to remove all high molecular weight molecules. This method is the subject of the Lentz '713 patent, discussed below. This induced remission, but required very expensive replacement of the albumin and left the patient's immunoglobulin at very low levels, thereby leaving him unprotected against infection.

Subsequent studies indicated that it was not an immunoglobulin complex protecting the tumors, and Dr. Lentz found that he could leave the immunoglobulin, allowing the patient to thereby retain better immunity. This was achieved by using a filter with a molecular weight cutoff of 120,000 daltons, instead of 150,000.

Further studies indicated that tumors produced low molecular weight molecules that were fragments of cytokine receptors, which were produced in large quantities in the blood, where they bound to the cytokines, preventing them from complexing with the tumor cells, leading to their death. Dr. Lentz then designed specific antibody columns, which selectively removed these inhibitors, inducing remission in tumor patients. The studies currently in progress remove three inhibitors: soluble tumor necrosis receptor 1, soluble tumor necrosis receptor 2, and a soluble cytokine receptor. The advantage of the selective removal is that the patient does not need either the albumin or immunoglobulin replaced, greatly lowering the cost of treatment, with the same or better efficacy.

*Legal Standard for Rejections Under 35 U.S.C. § 103*

The law is quite clear that, for the Patent Office to establish a *prima facie* case of obviousness of claimed subject matter, the prior art references relied upon must provide *both* a suggestion to make the claimed invention and a reasonable expectation of success. It is also clear



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that the whole field of the invention must be considered, including those publications which teach away from the claimed invention. Particularly relevant to the matters under consideration here are the decisions of the Court of Appeals for the Federal Circuit in *In re Dow Chemical*, 5 USPQ2d 1529 (1988) and *In re Vaeck*, 20 USPQ2d 1438 (1991). The *Dow* Court noted that:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art.... Both the suggestion and expectation of success must be founded in the prior art, not in the applicant's disclosure.
>
> In determining whether such a suggestion can fairly be gleaned from the prior art, *the full field of the invention must be considered*: for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention.... Evidence that supports, rather than negates, patentability must be fairly considered.

5 USPQ 2d at 1531-1532 (Citations omitted, emphasis added).

In *In re Dow Chemical*, a combination of three components forming an impact resistant rubber-based resin was not found to be obvious based upon art disclosing the individual components. The court noted that the record had shown that the claimed combination had previously been made, *but did not produce the product desired.* "That there were other attempts, and various combinations and procedures tried in the past, does not render obvious the later successful one.... Recognition of need, and difficulties encountered by those skilled in the field, are classical indicia of unobviousness," *Id.* at 1531 (citations omitted). The Court found that none of







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the prior art cited by the Applicant and the PTO suggested that any process could be used successfully in this three-component system to produce the product having the desired properties. Further, the Court stated that evidence from an expert expressing skepticism as to the success of the claimed combination before these inventors proved him wrong should be considered. *Id.* at 1532.

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

*The Prior Art*

Lentz

Lentz describes removal of a large number of proteins using a filter. The only selectivity is by virtue of the molecular weight cutoff of the filter, which is approximately 200,000. ALL proteins in the plasma with the possible exception of some IgM will pass through a filter with a cutoff of 200,000.

Selinsky does not make up for the deficiency of Lentz. Lentz teaches away from the selective removal of soluble cytokine receptor molecules. See col. 6, lines 34 to 46, of Lentz, which states that there are two inhibitors being removed, one, an IgG immunoglobulin type molecule (lines 39-44) and the other which is believed to be a high molecular weight compound





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(mw between 200,000 and 1,000,000). Neither could possibly be construed to be a soluble cytokine inhibitor such as soluble TNF receptor, which has a significantly lower molecular weight. Moreover, Lentz clearly does not know what the inhibitor(s) are, indicating that there are multiple inhibitors. In summary, Lentz teaches one of ordinary skill in the art that (1) the inhibitors are high molecular weight proteins and (2) there are more than one inhibitors involved in immunosuppression of the anti-tumor response, neither of which is a cytokine type molecule.

Selinsky

In the related application, U.S.S.N. 09/709,045, Examiner Lorraine Spector has indicated that Selinsky is not available as prior art since it was not received by the U.S. Patent Office until May 28, 1998, six days after the priority application was filed on May 22, 1998.

Selinksky describes an experiment to correlate the levels of soluble tissue necrosis factor receptor ("sTNFR") with tumor burden. This in no way makes obvious the removal of sTNFR to treat tumors or other disorders. The standard under 35 U.S.C. 103 is whether the prior art leads one of ordinary skill in the art to combine the prior art as applicant has done, ***with a reasonable expectation of success.***

The prior art at the time this application was filed in May 1998, was that there were a number of tumor markers that correlated with tumor burden. The most well known include the prostate specific antigen ("PSA") and carcinoembryonic antigen ("CEA"). Studies had been conducted to remove both PSA and CEA, with the hope of decreasing tumor burden. Neither had been effective. Therefore, one skilled in the art would have had no expectation of success that removal of a soluble cytokine receptor such as sTNFR would be effective.

Indeed, this is clearly the opinion shared by the authors of the paper. The Declaration under 37 C.F.R. 1.132 filed in U.S.S.N. 09/444,144, which subsequently issued as U.S. Patent



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No. 6,379,708 to Howell, et al., distinguished the same art, one of which was their own. Please see pages 2-3 of the declaration, discussing first the Lentz patent and then the Selinksky paper. As the authors of the Selinsky paper noted:

> "It is submitted that, although the statement in Selinsky et al. may cause one of skill in the art to consider how to antagonize or remove sTNFR1 *in situ*, such a statement is merely an invitation to experimentation and opens the door for one of skill in the art to consider a wide range of possible approaches. Indeed, Selinsky et al. provides absolutely no guidance as to how one of skill in the art would go about such a task, but rather generally state that the "therapeutic utility of manipulating sTNFRI levels *in vitro* has been demonstrated" and that "sTNFRI effectively inhibits immune responses *in vivo* and ...its modulation is a legitimate therapeutica avenue."
>
> It is submitted that one of skill in the art, when presented with an invitation to manipulate the effects of a soluble protein, would look to a variety of conventional approaches to remove or manipulate the effects of that soluble protein *in vivo*, because such approaches are the most clinically desirable means of treating a patient."

For the same reasons that the examiner allowed the claims in the Howell patent over the combination of Lentz and Selinsky, so are the claims in this application allowable over Lentz and Selinsky.

Okarma



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Lentz and Selinsky are discussed above. Okarma does not make up for the deficiencies of Lentz and Selinsky. Okarma does no more than describe immunoaffinity columns for removal of cytokines for treatment of disorders such as septic shock.

Feinman

**Relying solely on the examiner's summary of this reference, for which neither a citation nor a copy was received, it appears that it says that TNF is an important mediator of tumor killing and that gamma interferon can to be used to increase killing of target cells to TNF.**

This is a well known phenomena *in cell culture* and numerous efforts have been made to use TNF in the treatment of cancers, all unsuccessful due to the toxicity of TNF and because even with the high toxicity, administration of TNF was not effective in treatment of cancers, presumably due to the complexity of the process and that many factors were involved. Accordingly, Feinman teaches away from either TNF alone being successful due to its toxicity, or from the efficacy of targeting only TNF. There is no teaching that removal of soluble receptors of TNF would result in endogenous TNF suddenly becoming effective in treatment of the cancer. There is no indication of how Feinman would be applied to actual treatment of a patient.

Van Zee

**Again relying solely on the examiner's summary of this reference, for which neither a citation nor a copy was received, it appears that it says that soluble TNF receptors block TNF activity.**





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This reference teaches away from what is claimed. Selinksky fails to provide any evidence that selective removal of soluble TNF results in killing of tumors. This reference does not make up for that deficiency.

The standard under 35 U.S.C. is whether one skilled in the art would be led by the references to combine the prior art, as applicants have done, with a reasonable expectation of success. Nothing cited by the examiner leads one to expect that removal solely of soluble cytokine receptors, such as soluble TNF receptors, will lead to tumor regression. The examiner is using hindsight alone to arrive at the claimed methods. The quote from Selinksy at page 8 of the examiner's action makes this abundantly clear!

Maraskovsky

Maraskovsky describes the use of antibody columns to remove **antigens.** Certainly this technology was well known as of the priority date of this application. There is no teaching, however, of which antibodies to put into the antibody column, nor any teaching that would lead one to combine Maraskovsky with Selinsky, et al.

Lentz is of no further help in this regard. Lentz only discloses the use of filtration, not antibody columns, and indeed, as discussed above, provides no indication of the agents to be removed other than that they are high molecular weight, which *teaches away from the removal of the low molecular weight soluble TNF receptors.*

*The Prior Art does not Make the Claimed Methods Obvious*

The prior art fails to teach one of ordinary skill in the art, with a reasonable expectation of success, that one should remove soluble cytokine receptors, my any means, much less an immunoabsorbent column, to treat a disease such as cancer. Lentz teaches that if one removes every protein in the plasma having a molecular weight of about 48,000 (albumin) or larger,







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tumor reduction will occur. Selinsky merely observes that one can reduce TNFR levels in antibodies - not that the removal will be effective to treat cancer.

The test under 103 is whether one skilled in the art would be led, by the reference, to combine the references, as applicant has done, with a reasonable expectation of success. There is simply nothing in these references that leads one to that conclusion. The result is simply too unpredictable. Applicant has now conducted numerous trials in humans with a variety of different cancers, and shown that selective removal of soluble cytokines such as sTNFR1 and sTNFR2 does result in an inflammatory response resulting in substantial decrease in tumor volume. This is enhanced by treatment with other types of therapy, including chemotherapy, hyperthermia, and radiation.

The prior art, in combination, says that one should remove ***many proteins, including soluble cytokines*** (which are of a lower molecular weight than albumin) if one wants to treat tumors. Selinsky is merely an invitation to experiment, a discussion of an interesting observation – not a showing that sTNFR could be removed and cause tumor reduction. The prior art provides numerous examples of other tumor burden markers whose removal does not correlate with tumor reduction. The results obtained by applicant are simply too unpredictable.

Claim 5 requires treating the tissue with an agent selected from the group consisting of anti-angiogenic compounds, procoagulant compounds, cytokines, chemotherapeutic agents, and radiation. None of the art cited by the examiner provides any teaching that would lead one to treat patients, particularly patients who have already failed treatment with chemotherapeutic agents, to be treated again with these agents. However, applicant's studies have demonstrated that these additional agents, following or administered with the selective removal of the inhibitors, does impart additional benefit.





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Claim 6 defines the cytokine as GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF. None of the prior art teaches that one should remove soluble inhibitors of these molecules. Indeed, none of the art even mentions inhibitors of these cytokines.

None of the art teaches removing a cytokine receptor using an antibody column, as required by claims 8, 9, 10, 12, and 16-19. Selinsky only measures the presence of soluble tumor necrosis factor in cell culture. Lentz only discloses filtration.

**Submission of Declaration under 37 C.F.R. 1.131 and Request for Interference**

In the related application, U.S.S.N. 09/709,045, Examiner Lorraine Spector has indicated that Selinsky is not available as prior art since it was not received by the U.S. Patent Office until May 28, 1998, six days after the priority application was filed on May 22, 1998.Solely to facilitate declaration of an interference, and since the examiner has relied upon the Selinsky reference to support all of the rejections under 35 U.S.C. 103, enclosed is a Declaration by Dr. Lentz establishing that prior to publication of the Selinsky reference, he had conceived of the claimed method, disclosed it to the undersigned for purposes of filing a patent application, and that it was diligently reduced to practice upon filing of a patent application on May 22, 1998. The signed Declaration will be forwarded shortly.

This declaration should not be construed as an admission that there is no earlier disclosure of the subject matter nor that additional evidence may not be relied upon in an interference proceeding with U.S. Patent No. 6,379,708 to Howell, which is an issued U.S. patent, discloses and claims common subject matter. Howell was issued only after filing of a declaration under 37 C.F.R. 1.131 (one which the undersigned believes was clearly defective). Applicant requests declaration of an interference to resolve the issue of who is entitled to a patent. Howell's earliest priority date is November 20, 1999. This application claims priority as







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a continuation of U.S.S.N. 09/316,226 filed May 21, 1999, which is a continuation in part of U.S.S.N. 09/083,307 filed May 22, 1998. Accordingly, Lentz should be declared the senior party.

A proposed count is as follows:

A method of stimulating an immune response in a mammal having a pathological condition comprising:

Contacting the acellular component of blood from a mammal with a binding partner capable of specifically binding to a targeted immune system inhibitor selected from the group consisting of soluble receptors for tumor necrosis factor, interleukin-1 receptor antagonist, soluble receptor for interferon-gamma, soluble receptors for interleukin-1 and soluble receptors for interleukin-6,

Removing the binding partner bound to the targeted immune system inhibitor from the acellular component to produce an altered acellular component having a reduced amount of the targeted immune system inhibitor, and

Administering the altered acellular component, or blood combined with altered acellular component, to the mammal.

This count corresponds to all claims of Howell. Claims 37-44 are further restricted to where the means for binding the targeted immune system inhibitor is an antibody bound to an inert medium to form an absorbent matrix.

This count corresponds to claims 1-4 and 8-10 of the present application.







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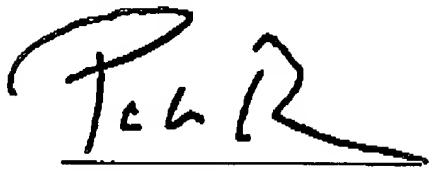
For the foregoing reasons, claims 1-6, 8-10, 12 and 16-20 should be allowed and an interference declared.

Respectfully submitted,



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